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PRO-ADDICTIVE AND ANTI-ADDICTIVE FACTORS FOR DRUG DEPENDENCE

KIYOFUMI YAMADA

*Department of Neuropsychopharmacology and Hospital Pharmacy,
Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan*

ABSTRACT

Drug dependence is defined as a chronically relapsing disorder that is characterized by compulsive drug taking, inability to limit intake, and intense drug cravings. The positive reinforcing/rewarding effects of drugs primarily depend on the mesocorticolimbic dopamine system innervating the nucleus accumbens while the craving for drugs is associated with activation of the prefrontal cortex. The chronic intake of drugs causes homeostatic molecular and functional changes in synapses, which may be critically associated with the development of drug dependence. Recent studies have demonstrated that various cytokines and proteinases are produced in the brain on treatment with drugs of abuse, and play a role in drug dependence. These endogenous modulators of drug dependence are divided into two groups, pro-addictive and anti-addictive factors. The former including tissue plasminogen activator, matrix metalloproteinase (MMP)-2 and MMP-9 act to potentiate the rewarding effects of drugs, while the latter such as tumor necrosis factor- α and glial cell line-derived neurotrophic factor reduce the reward. These findings suggest that an imbalance between pro-addictive and anti-addictive factors contributes to the development and relapse of drug dependence. Targeting these endogenous modulators would provide new therapeutic approaches to the treatment of drug dependence.

Key Words: Drug dependence, tPA, MMP, TNF- α , GDNF

INTRODUCTION

Drugs of abuse are chemically divergent with distinct primary targets of action. Repeated intake of any drug of abuse, however, results in many common features of drug dependence. Activation of mesocorticolimbic dopamine system, that originates in the midbrain ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc), prefrontal cortex and other limbic areas, has been implicated in the positive reinforcing (rewarding) effects of drugs of abuse.¹⁻⁴⁾ Psychostimulants, including cocaine (COCA), amphetamine (AMPH) and methamphetamine (METH), act as an indirect dopamine agonist at dopamine receptors: COCA increases extracellular dopamine levels by inhibiting dopamine transporters (DAT) whereas AMPH and METH stimulate dopamine release.^{5,6)} On the other hand, morphine (MORP) increases dopaminergic neurotransmission in the NAc via the activation of dopamine cells in the VTA, an area that possesses a high density of μ -opioid receptors. This activation results mainly from the disinhibition of inhibitory GABAergic interneurons in the VTA.^{7,8)}

Corresponding author: Kiyofumi Yamada, Ph.D.

Department of Neuropsychopharmacology and Hospital Pharmacy,

Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan

E-mail: kyamada@med.nagoya-u.ac.jp

Table 1 Role of tPA, TNF- α and GDNF in drug dependence

	METH	COCO	NICO	MORP	Alcohol
tPA	↑	N.D.	↑	↑	↑
TNF- α	↓	N.D.	N.D.	↓	N.D.
GDNF	↓	↓	N.D.	↓	↓

↑: Pro-addictive, ↓: Anti-addictive, N.D.: not determined

Once drug dependence has developed, it can be a life-long condition under which individuals show compulsive drug taking, intense cravings, and vulnerability to relapse even after years of abstinence. Regarding the long-lasting abnormalities in drug dependence, it has been reported that repeated exposure to AMPH in rats produces a long-lasting increase in the length of dendrites, and the number of branched spines,⁹⁾ and interferes with the ability of experience in a complex environment to increase dendritic arborization and spine density in the NAc and prefrontal cortex.¹⁰⁾ We have demonstrated that repeated METH treatment results in a long-lasting impairment of novelty-induced extracellular signal-regulated kinase 1/2 activation in the prefrontal cortex in mice.¹¹⁾ These structural and functional abnormalities may contribute to long-term behavioral consequences of drug abuse including drug dependence, psychosis, and cognitive impairment.

Chronic drug exposure induces the expression of various neurotrophins, cytokines, and proteinases in the brain, which plays a crucial role in the development and relapse of drug dependence.¹²⁻¹⁴⁾ These endogenous modulators of drug dependence are functionally classified into two groups, pro-addictive and anti-addictive factors.¹²⁾ The former, including tissue plasminogen activator (tPA),^{15,16)} matrix metalloproteinase (MMP)-2 and MMP-9,¹⁷⁾ act to potentiate the rewarding effects of drugs, while the latter such as tumor necrosis factor- α (TNF- α)¹⁸⁾ and glial cell line-derived neurotrophic factor (GDNF)^{19,20)} reduce the reward. In this review article, I review the role of these endogenous modulators in drug dependence (Table 1).

tPA/plasmin

tPA, a serine protease that catalyzes the conversion of plasminogen to plasmin, plays an important role in fibrinolysis. tPA is also abundantly expressed in the central nervous system, where it is stored in synaptic vesicles and released into the extracellular space by depolarization.²¹⁻²³⁾ Accumulating evidence has demonstrated that tPA plays a role in numerous aspects of synaptic plasticity and remodeling, including neurite outgrowth and neuronal development, the late phase of long-term potentiation, and memory.²⁴⁻²⁶⁾ Moreover, recent studies suggest that tPA acts as a modulator of neurotransmission and synaptic plasticity by impacting on glutamatergic and dopaminergic pathways.²⁷⁻²⁹⁾

A single injection of MORP in rats and mice induces tPA mRNA and protein expression in MAP2-positive neuronal cells in a naloxone-sensitive manner, which is associated with an increase in the enzyme activity in the NAc.¹⁵⁾ Not only MORP but also other drugs of abuse such as METH, nicotine (NICO) and ethanol increase tPA expression and activity in the NAc.^{16,30,31)} Furthermore, these drugs of abuse promote the release of tPA from postsynaptic neurons into the extracellular space in the NAc by stimulating dopamine D1 and D2 receptors.^{30,32)} Notably, dopamine D1 receptor/protein kinase A (PKA) signaling plays a major role in the regulation of tPA release in the NAc.³²⁾

Behavioral analyses with tPA-deficient [tPA(-/-)] and plasminogen-deficient [plg(-/-)] mice revealed that the tPA/plasmin system plays a crucial role in the rewarding effects of MORP,^{15,33,34)}

METH¹⁶⁾, and NICO.³⁰⁾ Behavioral sensitization to MORP and METH induced by repeated administration is suppressed in tPA-(-/-) mice.^{15,16)} Furthermore, seizures after ethanol withdrawal are suppressed in tPA-(-/-) mice, suggesting a role for tPA in the development of physical dependence on ethanol.³¹⁾ Accordingly, tPA is regarded as a pro-addictive factor for psychological and physical dependence.

An *in vivo* microdialysis-based study revealed that MORP- and NICO-induced dopamine release in the NAc was markedly decreased in tPA-(-/-) mice, but the deficit was restored by prior microinjection of recombinant tPA or plasmin into the NAc. These findings suggest that the tPA/plasmin system has a role in regulating dopamine release evoked by MORP and NICO in the NAc.^{15,30)} Of note, the tPA/plasmin system contributes to the depolarization-induced release of dopamine in the NAc.²⁸⁾ As a target of the tPA/plasmin system in regulating dopamine release in the NAc, protease-activated receptor-1 (PAR1-1) has been identified.^{30,35)} Regarding the METH-induced release of dopamine in the NAc, the expression of tPA in the NAc after repeated METH treatment is related to the development of sensitization in DAT-mediated METH-induced dopamine release via plasmin.³⁶⁾

TNF- α

TNF- α , an inflammatory cytokine produced by macrophages and circulating monocytes, affects brain function directly or indirectly through stimulation of vagal afferents.³⁷⁾ METH induces TNF- α gene expression in the brain of C57BL/6 mice³⁸⁾ and in human brain endothelial cells.³⁹⁾ Repeated METH treatment increases TNF- α mRNA and protein levels in neurons of the NAc through the activation of dopamine receptors.¹⁸⁾ Recombinant TNF- α inhibits METH-induced reward, discriminative stimulus effects, and dopaminergic neurotoxicity. Conversely, responses to METH are enhanced in TNF- α -deficient [TNF-(-/-)] mice. Furthermore, TNF- α attenuates DAT-mediated METH-induced dopamine release in the NAc, and potentiates striatal dopamine uptake into synaptosomes *in vitro* and *in vivo*. This neuroactive cytokine activates vesicular dopamine uptake by itself, and diminishes the METH-induced decrease in vesicular dopamine uptake. It is proposed that TNF- α plays a neuroprotective role in METH-induced drug dependence and neurotoxicity by activating plasmalemmal DAT as well as vesicular monoamine transporter-2 (VMAT-2), and inhibiting METH-induced dopamine release.¹⁸⁾

A recent study demonstrated that repeated MORP treatment increases TNF- α expression in the NAc and striatum, and TNF-(-/-) mice show enhanced MORP reward, indicating that TNF- α acts to reduce MORP reward.⁴⁰⁾ Interestingly, TNF- α induces GDNF expression in cultured neurons *in vitro*,⁴¹⁾ suggesting an interaction between anti-addictive factors (see below).

GDNF

GDNF enhances the survival and growth of dopaminergic neurons after injury *in vivo*.⁴²⁻⁴⁴⁾ This cytokine exerts biological activity via Ret and GDNF-family receptor- α (GFR α 1) receptors. The Ret receptor is shared by all four members of the GDNF family of growth factors and the specificity for GDNF is conferred by GFR α 1. GDNF activates Ret tyrosine kinase by first binding the cognate GFR α 1.⁴⁵⁾

Infusion of GDNF into the VTA blocks biochemical adaptations to chronic COCA treatment (induction of tyrosine hydroxylase, NR1 subunit of NMDA receptors, Δ FosB and PKA catalytic subunit), which is associated with the reduction of COCA reward.¹⁹⁾ Conversely, responses to COCA are enhanced in rats by intra-VTA infusion of anti-GDNF antibody and in GDNF-(+/-) mice. Chronic COCA treatment has no effect on GFR α 1 and Ret protein levels in the mesolimbic dopamine system, but significantly reduces phosphorylated Ret levels. These results suggest a feedback loop, whereby chronic COCA treatment decreases GDNF signaling in the VTA, which

then increases the behavioral sensitivity to subsequent drug exposure.¹⁹⁾

In agreement with the findings described above, a recent study supports a role for GDNF in the VTA in countering the addictive effects of alcohol. Thus, microinjection of GDNF into the VTA significantly suppresses alcohol consumption.^{14,46)} A putative anti-addiction drug Ibogaine increases GDNF mRNA and protein expression and activates GDNF signaling, which is associated with the desirable action of reducing alcohol consumption.⁴⁷⁾ Furthermore, GDNF-(+/-) mice show enhancement of MORP reward compared with wild-type littermates.⁴⁸⁾ Accordingly, it is suggested that GDNF acts as an anti-addictive cytokine in COCA, alcohol, and MOPR dependence.^{12,14)}

We have investigated a role for GDNF in the development and relapse of METH dependence by using intravenous self-administration and the reinstatement of drug-seeking behavior in GDNF-(+/-) mice, respectively.²⁰⁾ The results indicated that GDNF potentiates METH self-administration, enhances motivation to take METH, increases vulnerability to drug-primed reinstatement, and prolongs the cue-induced reinstatement of extinguished METH-seeking behavior. In contrast, there is no significant difference in novelty responses, METH-induced hyperlocomotion and sensitization, food-reinforced operant behavior and motivation, or reinstatement of food-seeking behavior between GDNF-(+/-) and wild-type littermates. Our findings suggest that GDNF is a potent anti-addictive factor involved in the development and relapse of METH dependence.²⁰⁾

CONCLUSION AND REMARKS

Various cytokines and proteinases are produced in the brain on treatment with drugs of abuse, and act as either pro-addictive or anti-addictive factors. Pro-addictive factors potentiate the rewarding effects of drugs of abuse, and thereby act to facilitate the development of drug dependence. Anti-addictive factors reduce the drug reward, and thus act to prevent the development of drug dependence. A potent anti-addictive factor GDNF is involved in not only the development but also the relapse of drug dependence. There may be interactions within and between pro-addictive and anti-addictive factors. I propose that changes in the balance between pro-addictive and anti-addictive factors in the brain play a crucial role in the development and relapse of drug dependence. Regulation of these endogenous modulators could be useful for the treatment of drug dependence.

REFERENCES

- 1) Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. *Neuron*, 1998; 21: 467–476.
- 2) Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron*, 2000; 25: 515–532.
- 3) Nestler EJ. Is there a common molecular pathway for addiction? *Nat Neurosci*, 2005; 8: 1445–1449.
- 4) Mizoguchi H, Yamada K, Mizuno M, Mizuno T, Noda Y, Nitta A, Nabeshima T. Regulation of methamphetamine reward by extracellular signal-regulated kinase 1/2/ets-like gene-1 signaling pathway via the activation of dopamine receptors. *Mol Pharmacol*, 2004; 65: 1293–1301.
- 5) Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol*, 1993; 33: 639–677.
- 6) Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci*, 1992; 13: 177–184.
- 7) Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J Neurosci*, 1992; 12: 483–488.
- 8) Bonci A, Williams JT. Increased probability of GABA release during withdrawal from morphine. *J Neurosci*, 1997; 17: 796–803.
- 9) Robinson TE, Kolb B. Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons

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- produced by previous experience with amphetamine. *J Neurosci*, 1997; 17: 8491–8497.
- 10) Kolb B, Gorny G, Li Y, Samaha AN, Robinson TE. Amphetamine or cocaine limits the ability of later experience to promote structural plasticity in the neocortex and nucleus accumbens. *Proc Natl Acad Sci USA*, 2003; 100: 10523–10528.
 - 11) Kamei H, Nagai T, Nakano H, Togan Y, Takayanagi M, Takahashi K, Kobayashi K, Yoshida S, Maeda K, Takuma K, Nabeshima T, Yamada K. Repeated methamphetamine treatment impairs recognition memory through a failure of novelty-induced ERK 1/2 activation in the prefrontal cortex. *Biol Psychiatry*, 2006; 59: 75–84.
 - 12) Yamada K, Nabeshima T. Pro- and anti-addictive neurotrophic factors and cytokines in psychostimulant addiction. mini review. *Ann NY Acad Sci*, 2004; 1025: 198–204.
 - 13) Yamada K, Nagai T, Nabeshima T. Drug dependence, synaptic plasticity, and tissue plasminogen activator. *J Pharmacol Sci*, 2005; 97: 157–161.
 - 14) Ron D, Janak PH. GDNF and addiction. *Rev Neurosci*, 2005; 16: 277–285.
 - 15) Nagai T, Yamada K, Yoshimura M, Ishikawa K, Miyamoto M, Hashimoto K, Noda Y, Nitta A, Nabeshima T. Tissue plasminogen activator-plasmin system participates in the rewarding effect of morphine by regulating dopamine release. *Proc Natl Acad Sci USA*, 2004; 101: 3650–3655.
 - 16) Nagai T, Noda Y, Ishikawa K, Miyamoto Y, Yoshimura Y, Ito M, Takayanagi M, Takuma K, Yamada K, Nabeshima T. The role of tissue plasminogen activator in methamphetamine-related reward and sensitization. *J Neurochem*, 2005; 92: 660–667.
 - 17) Mizoguchi H, Yamada K, Niwa M, Mouri A, Mizuno T, Noda Y, Nitta A, Itohara S, Banno Y, Nabeshima T. Reduction of methamphetamine-induced sensitization and reward in matrix metalloproteinase-2 and -9 deficient mice. *J Neurochem*, 2007; 100: 1579–1588.
 - 18) Nakajima A, Yamada K, Nagai T, Uchiyama T, Miyamoto Y, Mamiya T, Nitta A, Mizuno M, Tran MH, Seto A, Yoshimura M, Kitaichi K, Hasegawa T, Saito K, Yamada Y, Seishima M, Sekikawa K, Kim HC, Nabeshima T. Role of tumor necrosis factor- α in methamphetamine-induced drug dependence and neurotoxicity. *J Neurosci*, 2004; 24: 2212–2225.
 - 19) Messer CJ, Eisch AJ, Carlezon WA, Whisler K, Shen F, Wolf DH, Westphal H, Collins F, Russell DS, Nestler EJ. Role for GDNF in biochemical and behavioral adaptation to drugs of abuse. *Neuron*, 2000; 26: 247–257.
 - 20) Yan Y, Yamada K, Niwa M, Nagai T, Nitta A, Nabeshima T. Enduring vulnerability to reinstatement of methamphetamine-seeking behavior in glial cell line-derived neurotrophic factor mutant mice. *FASEB J*, 2007; 21: 1994–2004.
 - 21) Gualandris A, Jones TE, Strickland S, Tsirka SE. Membrane depolarization induces calcium-dependent secretion of tissue plasminogen activator. *J Neurosci*, 1996; 16: 2220–2225.
 - 22) Zhang Y, Kanaho Y, Frohman MA, Tsirka SE. Phospholipase D1-promoted release of tissue plasminogen activator facilitates neurite outgrowth. *J Neurosci*, 2005; 25: 1797–1805.
 - 23) Lochner JE, Honigman LS, Grant WF, Gessford SK, Hansen AB, Silverman MA, Scalettar BA. Activity-dependent release of tissue plasminogen activator from the dendritic spines of hippocampal neurons revealed by live-cell imaging. *J Neurobiol*, 2006; 66: 564–577.
 - 24) Seeds NW, Basham ME, Haffke SP. Neuronal migration is retarded in mice lacking the tissue plasminogen activator gene. *Proc Natl Acad Sci USA*, 1999; 96: 14118–14123.
 - 25) Calabresi P, Napolitano M, Centonze D, Marfia GA, Gubellini P, Teule MA, Berretta N, Bernardi G, Frati L, Tolu M, Gulino A. Tissue plasminogen activator controls multiple forms of synaptic plasticity and memory. *Eur J Neurosci*, 2000; 12: 1002–1012.
 - 26) Mataga N, Mizuguchi Y, Hensch TK. Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator. *Neuron*, 2004; 44: 1031–1041.
 - 27) Nicole O, Docagne F, Ali C, Margail I, Carmeliet P, MacKenzie ET, Vivien D, Buisson A. The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling. *Nat Med*, 2001; 7: 59–64.
 - 28) Ito M, Nagai T, Kamei H, Nakamichi N, Nabeshima T, Takuma K, Yamada K. Involvement of tissue plasminogen activator-plasmin system in depolarization-evoked dopamine release in the nucleus accumbens of mice. *Mol Pharmacol*, 2006; 70: 1720–1725.
 - 29) Samson AL, Medcalf RL. Tissue-type plasminogen activator: a multifaceted modulator of neurotransmission and synaptic plasticity. *Neuron*, 2006; 50: 673–678.
 - 30) Nagai T, Ito M, Nakamichi N, Mizoguchi H, Kamei H, Fukakusa A, Nabeshima T, Takuma K, Yamada K. The rewards of nicotine: regulation by tissue plasminogen activator-plasmin system through protease activated receptor-1. *J Neurosci*, 2006; 26: 12374–12383.

- 31) Pawlak R, Melchor JP, Matys T, Skrzypiec AE, Strickland S. Ethanol-withdrawal seizures are controlled by tissue plasminogen activator via modulation of NR2B-containing NMDA receptors. *Proc Natl Acad Sci USA*, 2005; 102: 443–448.
- 32) Ito M, Nagai T, Mizoguchi H, Sato K, Hayase M, Otsuka N, Nabeshima T, Takuma K, Yamada K. Activation of postsynaptic dopamine D1 receptors promotes the release of tissue plasminogen activator in the nucleus accumbens via PKA signaling. *J Neurochem*, 2007; 103: 2589–2596.
- 33) Nagai T, Kamei H, Ito M, Hashimoto K, Takuma K, Nabeshima T, Yamada K. Modification by the tissue plasminogen activator-plasmin system of morphine-induced dopamine release and dopamine-dependent hyperlocomotion, but not antinociceptive effect in mice. *J Neurochem*, 2005; 93: 1272–1279.
- 34) Yan Y, Yamada K, Mizoguchi H, Noda Y, Nagai T, Nitta A, Nabeshima T. Reinforcing effects of morphine are reduced in tissue plasminogen activator (tPA)-knockout mice. *Neuroscience*, 2007; 146: 50–59.
- 35) Ito M, Nagai T, Mizoguchi H, Fukakusa A, Nakanishi Y, Kamei H, Nabeshima T, Takuma K, Yamada K. Possible involvement of protease-activated receptor-1 in the regulation of morphine-induced dopamine release and hyperlocomotion by the tissue-plasminogen activator-plasmin system. *J Neurochem*, 2007; 101: 1392–1399.
- 36) Fukakusa A, Nagai T, Mizoguchi H, Otsuka N, Kimura H, Kamei H, Kim HC, Nabeshima T, Takuma K, Yamada K. Role of tissue plasminogen activator in the sensitization of methamphetamine-induced dopamine release in the nucleus accumbens. *J Neurochem*, 2008; 105: 436–444.
- 37) Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev*, 1998; 105: 83–107.
- 38) Flora G, Lee YW, Nath A, Maragos W, Hennig B, Toborek M. Methamphetamine-induced TNF- α gene expression and activation of AP-1 in discrete regions of mouse brain: potential role of reactive oxygen intermediates and lipid peroxidation. *Neuromolecular Med*, 2002; 2: 71–85.
- 39) Lee YW, Hennig B, Yao J, Toborek M. Methamphetamine induces AP-1 and NF- κ B binding and transactivation in human brain endothelial cells. *J Neurosci Res*, 2001; 66: 583–591.
- 40) Niwa M, Nitta A, Yamada Y, Nakajima A, Saito K, Seishima M, Noda Y, Nabeshima T. Tumor necrosis factor- α and its inducer inhibit morphine-induced rewarding effects and sensitization. *Biol Psychiatry*, 2007; 62: 658–668.
- 41) Niwa M, Nitta A, Yamada Y, Nakajima A, Saito K, Seishima M, Shen L, Noda Y, Furukawa S, Nabeshima T. An inducer for glial cell line-derived neurotrophic factor and tumor necrosis factor- α protects against methamphetamine-induced rewarding effects and sensitization. *Biol Psychiatry*, 2007; 61: 890–901.
- 42) Lin LF, Doherty DH, Lile JD, Bektess S, Collin F. GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. *Science*, 1993; 260: 1130–1132.
- 43) Beck KD, Valverde J, Alexi T, Poulsen K, Moffat B, Vandlen RA, Rosenthal A, Hefti F. Mesencephalic dopaminergic neurons protected by GDNF from axotomy-induced degeneration in the adult brain. *Nature*, 1995; 373: 339–341.
- 44) Tomac A, Lindqvist E, Lin LF, Ogren SO, Young D, Hoffer BJ, Olson L. Protection and repair of the nigrostriatal dopaminergic system by GDNF in vivo. *Nature*, 1995; 373: 335–339.
- 45) Airaksinen MS, Saarma M. The GDNF family: signalling, biological functions and therapeutic value. *Nat Rev Neurosci*, 2002; 3: 383–394.
- 46) He DY, McGough NN, Ravindranathan A, Jeanblanc J, Logrip ML, Phamluong K, Janak PH, Ron D. Glial cell line-derived neurotrophic factor mediates the desirable actions of the anti-addiction drug ibogaine against alcohol consumption. *J Neurosci*, 2005; 25: 619–628.
- 47) He DY, Ron D. Autoregulation of glial cell line-derived neurotrophic factor expression: implications for the long-lasting actions of the anti-addiction drug, Ibogaine. *FASEB J*, 2006; 20: 2420–2422.
- 48) Niwa M, Nitta A, Shen L, Noda Y, Nabeshima T. Involvement of glial cell line-derived neurotrophic factor in inhibitory effects of a hydrophobic dipeptide Leu-Ile on morphine-induced sensitization and rewarding effects. *Behav Brain Res*, 2007; 179: 167–171.